REMARKS/ARGUMENTS

The foregoing amendments to the specification confirm that all deposits were made under the terms of the Budapest Treaty, and meet all criteria set forth in 37 C.F.R. §§1.801-1.809.

Claims 21 and 26-31 are pending in this application, and stand rejected on various grounds. Applicants note the withdrawal of the previous rejection of Claims 21 and 26 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

The following new grounds for rejection have been raised in the present Office Action.

Claim Rejections – 35 U.S.C. §112

(1) Claims 21, and 26-31 (all claims pending) were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly "does not reasonably provide enablement for a method for identifying a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer, wherein the patient's tumor cells express HER2 antibody at a **0 or 1+** level by immunohistochemistry." (Emphasis original.) While acknowledging enablement for the treatment of patients whose tumor cells express HER2 at a 2+ or 3+ level by immunohistochemistry, the Examiner asserts that "no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in treating breast cancer that does not overexpress HER2."

The Examiner argues that, apart from the correlation disclosed in the specification between the FISH status and response to Herceptin® treatment for 2+ and 3+ subjects (Example 2), wherein the FISH+ subjects showed a much greater response to chemotherapy and Herceptin® than FISH- subject, suggesting FISH+ selection analysis in combination with IHC detection of HER2 overexpression provides a more accurate indicator of likelihood of success with Herceptin® treatment than for IHC analysis alone, "there is only a hypothesis that 0 and 1+ patients would also benefit from the treatment." In support of this assertion, the Examiner cites U.S. Patent No. 6,156,321 as allegedly teaching that among the drawbacks of antibody anti-tumor therapy is that antigen-negative cells can survive and repopulate a tumor. In addition, Lewis *et al.* (*Cancer Immunology Immunotherapy* 37:255-263 (1993)) is cited for its teaching, in

Table 2 in *in vitro* studies, that "while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected." The Examiner concludes that '[s]uccessful, effective administration of HER2 antibody to treat breast cancer in 0 and 1+ IHC level patients cannot be predicted based only on the hypothesis provided by the specification." According to the rejection, low expression levels of HER2 at the 0 and 1+ IHC level in a breast cancer patient "would suggest a lack of HER2 receptors present, and in the absence or near absence of receptor, it would not be expected that the antibody would be effective to treat, especially in view of the teaching in the art that effective treatment would not predictably expected at IHC levels less than 2+ or 3+."

Before turning to the specific reasons, it might be of benefit to spend some time explaining the invention, since some of the remarks appear to reflect a lack of appreciation or lack of full understanding of the invention claimed.

The invention concerns a method of identifying and treating breast cancer patients disposed to respond favorably to treatment with a HER2 antibody, huMAb4D5-8. The claimed method is directed to the treatment of patients whose tumor cells express HER2 at a 0 or 1+ level, after amplification of the *her2* gene is detected in tumor cells in a tumor sample of the patients.

As explained on page 5, lines 18-28 of the specification, according to current patient selection criteria, patients with 0 and 1+ IHC scores are not recommended for treatment with HER2 antibodies, while patients in the 2+ and 3+ IHC score groups are. Patients in the 3+ IHC subgroup show a 17% response rate to such treatment, which is very close to the response rate of patients whose tumors show amplification of the *her2* gene (FISH+ patients). In contrast, patients with an IHC score of +2 respond to HER2 antibody treatment with a response rate less than half of the response rate of patients whose tumors show amplification of the *her2* gene (FISH+ patients). Example 1, Table 1, additionally shows that 4% of the patients with a 0 IHC score were FISH+. From this, the present inventors recognized that the IHC analysis of HER2 protein levels unnecessarily excludes patients from HER2 antibody treatment, due to the noted anomalies in the IHC test. Thus, the present invention opens up the possibility for the treatment

of patients who are likely to benefit from HER2 antibody therapy but would not have been treated if diagnosed with immunohistochemistry methods, due to their 0 or 1+ IHC scores. The benefits of these findings for cancer patients can be hardly overstated. The present invention enables the selection of all patients who are likely to benefit from HER2 antibody treatment, and allows an early start of other treatments for patients who are not.

Turning to the rejection, the test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (M.P.E.P. §2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). Applicant submits that, based on the teaching of the present application meets this standard.

A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (M.P.E.P. §2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762 63 (2d Cir. 197 1), cert. Denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as

broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

The present invention is from the field of antibody-based cancer therapy. It has been well established that the level of skill in this field is high, and is represented by a Ph.D. scientist or an M.D., with several years of experience. In view of the extensive teaching provided in the specification for the preparation and use of HER2 antibodies, including huMAb4D5-8, to treat breast cancer patients (see, *e.g.,* page 10, lines 16-28; page 15, line 9 - page 16, line 8; and the Examples), detection of gene amplification an HER2 protein expression (page 17, line 24 - page 22, line 24; and the Examples); and pharmaceutical compositions and methods of treatment (page 22, line 26 - page 26, line 27) one of ordinary skill would know how to identify a patient whose tumor shows the specified characteristics, and treat such patient with a HER2 antibody huMAb4D5-8.

Applicants respectfully disagree with the Examiner's assertion that "[N]o one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in a cancer that does not overexpress HER2." An important finding underlying the claimed invention is that detection of *her2* gene amplification is a better indicator of patient response to treatment with a HER2 antibody than overexpression of the HER2 protein. One reason for this is that the processing of tissue samples, especially formalyn fixed, paraffin embedded samples, can disrupt or destroy antibody epitopes on the HER2 protein, but has less impact on gene amplification assays (see, the paragraph bridging pages 5 and 6 of the specification). Thus, low existing expression levels of HER2 in breast cancer patients (0 and 1+ IHC level if the patient is diagnosed by immunohistochemistry) do not necessarily mean "a lack of HER2 receptor present," or "the absence or near absence of receptor" as the Examiner suggests in the passage between pages 4 and 5 of the Office Action, rather, HER2 protein levels corresponding to a 0 or 1+ IHC score might just mean that the *her2* and HER2 protein are present, but the latter is not detected by IHC due to limitations of immunohistochemistry-based methods. The present invention provides methods and means for identifying and treating such patients, who would have been "missed" by relying on immunohistochemistry, and thus would not have been offered HER2 antibody treatment.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdrawn the present rejection.

(4)(b) Claims 4 and 13 were additionally rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate enablement. According to the rejection, while the specification provides enablement where the patient's tumor cells express HER2 at a 2 or 3 level by immunohistochemistry, does not reasonably provide enablement when the HER2 overexpression by immunohistochemistry is 0 or 1+.

The rejection is respectfully traversed.

In response to the previous rejection for alleged lack of enablement, Applicant has shown that Claim 1, reciting the treatment of subjects after it has been determined that the *her2* gene is amplified in their tumor cells, is enabled. Claims 4 and 13 depend from Claim 1, carrying its recitations, and are enabled for the same reason. Furthermore, the fact that earlier publications tied the administration of HER2 antibody therapy to HER2 overexpression does not negate the teachings of the present invention. As explained above, an important finding on which the present invention is based is that tying treatment to HER2 overexpression excludes from treatment a subgroup of patients, whose tumors would not show or would show only minor HER2 overexpression if diagnosis were based on immunohistochemistry (HERcepTest™), even though those of such patients whose tumor is characterized by *her2* amplification are reasonably expected to benefit from such treatment.

Accordingly, the reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 U.S.C. §103

(1) Claims 1, 2, 3, 5, 6, 7, 8, and 12 were rejected as allegedly obvious over Baselga I (*J. Clin Oncol,* 14:737-744 (1996)) or Baselga II (*Semin Oncol*, 26:78-83 (1999) in view of either Pauletti (*Oncogene*, 13:63-72 (1996) or Persons (*Annals of Clinical and Laboratory Science,* 30:41-48 (2000)). According to the rejection, Baselga I and Baselga II teach methods for treating breast cancer patients over-expressing HER2 with trastuzumab, therefore, they recognize that breast cancer patients should be screened for HER2 overexpression before

treatment to find patients who have the highest likelihood of responding to treatment. Pauletti and Persons were cited to show that "almost all patients that overexpress HER2 as determined by immunohistochemistry do so because of gene amplification. From this, the Examiner concludes that it would have been *prima facie* obvious to substitute the immunohistochemistry detection of HER2 expression by detection of *her2* gene amplification by FISH. According to the rejection, a motivation would have existed, since either Pauletti or Persons teaches the advantages of the FISH technique in assessing a patient's HER2 status, "therefore increasing the likelihood of effectiveness for anti-HER2 antibody cancer treatment by identifying and treating patients who overexpress HER2."

The rejection is respectfully traversed.

Both Baselga I and Baselga II teach that overexpression of HER2 plays an important role in the pathogenesis and poor prognosis of breast cancer. Thus, for example, Baselga I states: HER2 is overexpressed in 25% to 30% of human breast cancers and predicts for a worse prognosis in patients with primary disease that involves axillary lymph nodes." (Page 737, first column.) A similar statement is present in Baselga II at page 78, second column. Both Baselga I and Baselga II describe the treatment of HER2 overexpressing patients with HERCEPTIN® (trastuzumab, rhuMab4D5). Baselga I hypothesizes that since "in vitro studies suggest that those breast cancer cell lines that have the highest basal level of $p185^{HER2}$ [HER2] phosphorylation are most growth-inhibited by anti- $p185^{HER2}$ antibodies," an antibody "that specifically recognizes only overexpressed tyrosine-phosphorylated 185^{HER2}-positive tumors might prove useful in predicting the subset of $p185^{HER2}$-positive tumors most likely to respond to rhuMAb HER2." (Page 743, first column.) Baselga II confirms the importance of HER2 overexpression by providing clinical evidence that breast cancers overexpressing HER2 can be successfully treated with HERCEPTIN® (trastuzumab, rhuMab4D5). There is no mention in either of the primary references of *her2* amplification, or the use of *her2* amplification as an indicator of patient responsiveness to HER2 antibody treatment.

Pauletti *et al.* teach that amplification of the HER-2/*neu* gene is an important alteration in human breast cancer occurring in 25-30% of infiltrating ductal carcinomas, and carries important prognostic information. Pauletti compares detection and quantitation of HER-2/*neu* gene

amplification using FISH with immunohistochemistry. The authors emphasize the advantages of FISH is assessing formalin-fixed, paraffin-embedded tissue samples, and note that the "only potential disadvantage to FISH is represented by its 3.5% failure in sensitivity related to the fact that FISH does not assess HER-2/*neu* expression and therefore cannot detect those few cases which overexpress the gene product in the absence of gene amplification." (Page 68, second column.) In the same column, the authors add that HER-2/*neu* overexpression is rarely found in tumors with a single copy of the gene," therefore, this discrepancy is of little interest. It is clear from the entire disclosure that Pauletti *et al.* consider the detection of gene amplification a surrogate for HER-2 overexpression, and promote FISH for patient selection under the assumption that FISH will not miss any significant number of patients who could be treated with HER2 antibodies (*i.e.,* whose patients overexpress HER2 but contain a single copy of the *her2* gene). Similarly, Persons *et al.* teach that *her2* gene amplification parallels HER2 overexpression, and cites, with approval, Pauletti's finding that overexpression of HER is rare in the absence of her2 gene amplification.

Accordingly, when combining the teaching of Baselga I or Baselga II with Pauletti *et al.* or Persons *et al.,* one of ordinary skill would conclude that FISH is a better alternative to identify patients for HER2 antibody treatment when analysis is performed on formalin-fixed, paraffin-embedded tumor samples. There is nothing in these combinations that would teach that patients who would not qualify for HER2 antibody treatment based on immunohistochemistry, since their tumors would show no over low HER2 overexpression if tested by immunohistochemistry, could still be successfully treated with HER2 antibodies, if *her2* gene amplification is detected in their tumors. On the contrary, in view of the fact that Pauletti *et al.* and Persons *et al.* essentially equate HER2 overexpression and gene amplification, from the combined teaching of Baselga I or Baselga II and Pauletti *et al.* or Persons *et al.* one of ordinary skill at the time the present invention was made would have concluded that such situation does not exist.

Since the cited combination of references does not make the claimed invention obvious, the Examiner is respectfully request to withdraw the present rejection.

(2) Claims 9, 10 and 14 were rejected under as allegedly obvious over the combined references cited in the previous rejection in view of Burris III *et al.* (*Seminars in Oncology*,

27:19-23 (2000). Burris III was cited for its teaching that treatment with docetaxel demonstrated synergy with the anti-HER2 antibody trastuzumab.

The rejection is respectfully traversed.

Claims 9, 10, and 14 depend from Claim 1, carrying its recitations. In response to the previous rejection, Applicant has shown that the invention claimed in Claim 1 is not obvious over the combination of references that is further combined with Burris III in the present rejection. The inventions claimed in Claims 9, 10, and 14 are unobvious for the same reason, and the present rejection should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **P1829R1**).

Respectfully submitted,

Date: March 27, 2006

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